MEMORANDUM

TO: David P. Spath, Ph.D., Chief
Division of Drinking Water and Environmental Management Branch
Department of Health Services
601 North 7th Street, Mail Stop 92
P.O. Box 942732
Sacramento, California 94234-7320

VIA: George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs

VIA: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section

FROM: Robert A. Howd, Ph.D., Chief
Water Toxicology Unit
Pesticide and Environmental Toxicology Section

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SUBJECT: PROPOSED ACTION LEVEL FOR VANADIUM

Staff of the Office of Environmental Health Hazard Assessment (OEHHA) have reviewed the Department of Health Service's proposed action level of 50 μg/L of vanadium, derived from the U.S. Environmental Protection Agency's (U.S. EPA) Health Effects Assessment Summary Tables (HEAST), fiscal year (FY) 1997 (U.S. EPA, 1997). OEHHA does not concur with this proposed action level, and recommends that the action level be set at 15 μg/L of vanadium.

Vanadium is a naturally occurring "rare earth" element that is found ubiquitously in the earth's crust. While elemental vanadium does not occur in nature, vanadium compounds are found in fossil fuels and exist in over 50 different mineral ores. Vanadium has six different oxidation states (1-, 0, 2+, 3+, 4+, and 5+) of which the latter three are the most common.

The primary industrial use of vanadium is in the steel industry where it is used to strengthen steel. In the form of ferrovanadium alloys, vanadium is considered essential in the manufacture of jet aircraft engines. Small amounts of vanadium are also used in the manufacture of phthalic anhydride, sulfuric acid, pesticides, dyes, inks, pigments, and other chemicals.

On a daily basis, people are exposed to an estimated 10 to 60 micrograms of vanadium, with food contributing between 10 to20 micrograms per day. A daily vitamin pill also may contribute 10 μg/day. Human and animal data reveal that ingested vanadium is poorly absorbed from the gastrointestinal tract, and is mostly excreted, unabsorbed, in the feces. The major portion of absorbed vanadium is typically excreted in the urine with a biological half-life in humans of 20 to 40 hours. From animal studies, we can reasonably infer that low concentrations of absorbed vanadium can be apportioned to the kidney, bones, liver, and lungs of humans similarly exposed. However, there is no evidence that the ingestion of vanadium at these daily levels results in any adverse human health effects.

In our review of the scientific literature, we concluded that the underlying basis for the current level is inadequate. Specifically, the HEAST citation refers to the U.S. EPA's Health Effects Assessment for Vanadium and Compounds. This document clearly states that it is "a preliminary, interim assessment" and that all values cited, including the chronic oral reference dose (RfD), "should be considered preliminary and reflect limited resources." A review of this document confirms the preliminary basis of the assessment.

The Schroeder *et al.* (1970) study, which was used by U.S. EPA to derive its RfD, contains a number of flaws. First, this lifetime drinking water study on Long-Evans rats was conducted using only a single dose level of 5 ppm vanadium as vanadyl sulfate. Further, the authors reported an effect of uncertain biological significance. Female rats had statistically significant decreases in fasting serum cholesterol levels (which was attributed to chromium nutrient deficiency), while male rats had increased levels. Next, during the study, one third of the animals died from an epidemic of virulent pneumonia that struck the rat colony. Finally, the authors noted that the diet fed to the animals contained "relatively large amounts" of vanadium, but did not quantify these levels. Consequently, this study is of minimal use in establishing a definitive health-protective value.

A review of the documentation provided by the Agency for Toxic Substances and Disease Registry (ATSDR) shows that they have not set a chronic oral minimum risk level (MRL) for vanadium, but have set an intermediate-duration oral MRL of 0.003 mg/kg-day (ATSDR, 1991). This MRL was based on a three-month study on rats which were administered 0, 5, 10, or 50 ppm sodium metavanadate in drinking water (Domingo *et al.*, 1985). At the termination of the study all treated groups showed mild histological change in the kidney, lungs, and spleen that appeared dose-related. The no-observed-adverse-effects level (NOAEL) was set at 5 ppm of sodium metavanadate which is equivalent to 0.3 mg/kg-day of vanadium. ATSDR also applied a total uncertainty factor of 100 to account for extrapolation from rats to humans (10), and to account for sensitivity in humans (10). While this MRL could reasonably serve as a basis for the derivation of an action level if coupled with an appropriate modifying factor, OEHHA's recommendation is based on two other rationales.

The primary basis for OEHHA's recommendation of an action level of 15 µg/L for vanadium is to provide protection for unborn children and neonates. Animal data suggest that exposure to vanadium causes significant reductions in pup weight and length when administered to dams prior to mating, throughout gestation, and during lactation (Domingo *et al.*, 1986). In this study, male Sprague-Dawley rats were administered 0, 5, 10 and 20 mg/kg of sodium metavanadate by oral gavage for 60 days prior to mating. Females were similarly treated for 14 days prior to mating, then continued on this dosing regime through gestation and 21 days of lactation.

There were no signs of maternal toxicity, but pups at all dose levels displayed significantly lower weights that differed from controls by 11 to 28 percent ($p < 0.001$), and pup length was significantly reduced as compared to controls by 3 to 16 percent ($p < 0.05$-0.001). The results of this experiment demonstrate that a dose of at least 5 mg/kg-day of sodium metavanadate, which corresponds to 2.1 mg/kg-day of vanadium, may result in developmental effects for the offspring. The authors conclude that 2.1 mg/kg-day of vanadium is the lowest-observed-adverse-effect-level (LOAEL). The selection of this study as the basis for the derivation of the action level is supported by other developmental and reproductive studies which indicate that at high dose levels (7.5 to 30 mg/kg-day), vanadium can have adverse effects. The effects include reduced pup weight and length, increase in early resorptions, malformations (cleft palate), and reduced fertility (Paternain *et al.*, 1990; Sanchez *et al.*, 1991; Nava de Leal *et al.*, 1998; Llobet *et al.*, 1993).

A secondary basis for our recommendation comes from nutritional guidance which propose an estimated upper and lower daily limits for vanadium. Nutritionists have debated for years whether vanadium is an essential nutrient for human health. While vanadium deficiencies have not been identified in humans, extrapolation from animal studies indicates that an estimated daily dietary intake (EDDI) of vanadium can be set at 10 µg/day (Uthus and Seaborn, 1996). An EDDI is the level believed, but not proven, to be the amount needed by humans to maintain proper physiological function.

An upper recommended daily limit of 100 µg/day of vanadium for humans has been estimated by nutritionists (Uthus and Seaborn, 1996; Harland and Harden-Williams, 1994) who state that these daily levels should not be exceeded "except under medical supervision." Similarly, a toxicological review of vanadium has set an estimated upper boundary of 200 µg/day of vanadium as a "safe" intake level for humans based on a review of animal toxicology studies, including developmental (Domingo, 1996). Therefore, this upper exposure range of 100 to 200 µg/day of vanadium is intended to be protective of developing fetuses, neonates, and other sensitive populations. In fact, exposures of human adults show that doses up to at least 0.3 mg/kg-day of vanadium are not associated with any adverse human health effects (Fawcett *et al.*, 1997; Goldfine *et al.*, 2000).

OEHHA has determined that use of the 2.1 mg/kg-day LOAEL based on a developmental and reproductive rat study, and the use of a total uncertainty factor of 1,000 are appropriate for deriving an action level for vanadium. Therefore, the public health protective concentration (C) for vanadium of 15 µg/L in drinking water can be derived from the following equation:

$$C = \frac{\text{LOAEL x BW x RSC}}{\text{UF x DWC}} = \frac{\text{2.1 mg/kg-day x 70 kg x 0.2}}{\text{1,000 x 2 L/day}} = \text{0.0147 mg/L} = \text{15 µg/L}$$

where,

LOAEL	=	lowest-observed-adverse-effect-level,
BW	=	adult human body weight,
RSC	=	relative source contribution,
UF	=	uncertainty factor, and
DWC	=	adult daily drinking water consumption.

Based on the health protective concentration calculated, OEHHA recommends and supports an action level of 15 ppb (µg/L) for vanadium in drinking water. OEHHA believes the proposed action level of 15 µg/L of vanadium is protective of human health given long term exposure for the following reasons. The most sensitive, significant endpoint has been selected to derive the action level, and to that a 1,000-fold uncertainty factor has been added. This uncertainty factor accounts for extrapolation from animals to humans (10), extrapolation from a LOAEL to a NOAEL (10), and differences in human sensitivity (10). It is anticipated that persons drinking water containing 15 µg/L (representing 30 µg/day from consumption of 2 L/day of tap water) will not exceed the estimated daily upper boundary range of vanadium (200 µg/day), after addition of the other typical vanadium sources of 10 to 20 µg/day from food and 10 µg/day from vitamin supplements. The action level is also supported by a number of human and animal studies which show no adverse effects at higher doses and longer durations.

Should you have any questions about this review, please contact me at (510) 622-3168.

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